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(57) Abstract

This invention relates to the use of topical formulations of certain matrix metalloproteinase inhibitor compounds in treating psoriasis.

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Novel use of Matrix Metalloproteinase Inhibitors

Field of the Invention.

This present invention relates to the use of topical formulations of certain matrix metalloproteinase inhibitors (MMPIs) in treating psoriasis.

Background to the invention.

Psoriasis is a common, chronic inflammatory skin disorder affecting 1 - 3% of the world's population. It presents in many, varied forms including: plaque-type, guttate, generalised pustular, erythrodermic, flexural, palmar-plantar and nail, and the disease is usually described by its visual appearance.

Current psoriasis treatments include ultraviolet-B phototherapy treatment, or administration of: vitamin D_3 analogues, salicylic acid, synthetic retinoids, anthralin (dithranol), cyclosporine, glucocorticosteroids and coal tar preparations. Many of these agents require lengthy treatments and are often associated with poor patient compliance. No cure yet exists for psoriasis.

Despite extensive research, the underlying abnormality producing psoriatic lesions remains unconfirmed. Lesions are characterised by hyperproliferation of the epidermis, inflammatory cell accumulation and increased tortuosity and dilation of dermal papillary blood vessels. The majority of research studies have concentrated on the interplay between inflammatory cells and epidermal proliferation. Central to this are cytokines produced by activated keratinocytes which are thought to induce keratinocyte proliferation, lymphocyte migration and upregulation of adhesion molecules on vascular endothelium thus permitting lymphocyte recruitment. An early occurrence in the pathologic changes of psoriasis is the appearance of macrophages and T cells (especially activated T helper cells) in psoriatic skin lesions. Activated T cells have been shown to be capable of releasing cytokines that stimulate growth of normal keratinocytes.

Evidence suggests that the capillary changes seen during active psoriasis are the result of neovascularisation through endothelial cell proliferation (Wolf and Harrison, J. Invest. Dermatol. 59:40-43,1973) and that the epidermis is capable of inducing this proliferation possibly via production of one or more angiogenic factors (Nickoloff et al., Am. J. Pathol. 144:820-828, 1994).

A vital step in the proliferation of endothelial cells during neovascularisation is the digestion of basement membranes by the migrating endothelial cells. This process requires the presence of matrix degrading enzymes such as the matrix metalloproteinases. Inhibitors of matrix metalloproteinases have been implicated in inhibiting angiogenesis (Tamargo *et al.* (1991) Cancer Res. **51**:672-675; Fischer *et al.* (1994) Dev. Biol. **162**:499-510 and Galardy *et al.* (1994) Cancer Res. **54**:4715-4718).

The pathogenic mechanism of psoriasis is unclear, and good animal models do not yet exist, however, there are some similarities between psoriatic lesions and mouse skin following topical administration of an agent such as phorbol ester (PdiBu) or 12-O-tetradecanoylphorbol 13-acetate (TPA). Such administration induces biochemical and histopathological changes in mouse skin, such as leukocyte infiltration, epidermal hyperplasia, activatyion of protein kinase C and increased levels of interleukin 1.

Using such a model, Holleran *et al.*, (Arch. Dermatol. Res. 289:138-144, 1997) found that two matrix metalloproteinase inhibitors (GM6001 and GM 1489) were effective in inhibiting the inflammatory and hyperproliferative responses in the murine model of dermal inflammation and hyperproliferation. In these studies however, the test agent was administered only 15 minutes after the phorbol ester inducing agent application. According to Griffiths *et al.* (Agents and Actions. 25(3/4):344-351, 1988), topical application of the inducing agent (i.e TPA) produced maximal oedema approximately 6 hours after administration. Thus, whilst the test agents in Holleran et al. demonstrate inhibition of the PdiBu-induced onset of the oedema and inflammation, it remains uncertain whether or not these agents can reverse the psoriasis-like effects once they are established. To establish this it would be necessary to apply the test agent only after the inflammation and oedema have set in.

The matrix metalloproteinases (MMPs) constitute a family of calcium and zinc dependent endoproteinases which are characterised by the presence in the structure of a catalytic zinc atom. It is now known that there exists a range of metalloproteinase enzymes that include: collagenase-1 (MMP-1), 72 kDa-gelatinase (MMP-2), stromelysin-1 (MMP-3), matrilysin (MMP-7), neutrophil collagenase (MMP-8), 92 kDa-gelatinase (MMP-9;gelatinase B), stromelysin-2 (MMP-10), stromelysin-3 (MMP-11), macrophage metalloelastase (MMP-12), collagenase-3 (MMP-13), MT-MMP-1 (MMP-14), MT-MMP-2 (MMP-15), MT-MMP-3 (MMP-16), MT-MMP-4 (MMP-17), MMP-18 (MMP-19) and enamelysin. The MMPs are collectively capable of hydrolysing all the proteins of the extracellular matrix. Both natural and synthetic inhibitors of matrix metalloproteinases (MMPs) have been described (Brown and Giavazzi, 1995). Many known matrix metalloproteinase inhibitors (MMPIs) are peptide derivatives, based on naturally occurring amino acids, and are analogues of the cleavage site in the collagen molecule. Other known MMP inhibitors are less peptidic in structure, and may more properly be viewed as pseudopeptides or peptide mimetics. Such compounds usually having a functional group capable of binding to the zinc (II) site in the MMP, and known classes include those in which the zinc binding group is a hydroxamic acid, carboxylic acid, sulphydril, and oxygenated phosphorus (eg phosphinic acid and phosphonamidate including aminophosphonic acid) groups.

Beckett and Whittaker (Exp. Opin. Ther. Patents 8(3):259-282, 1998) review the developments in the design and clinical evaluation of various synthetic MMP inhibitors, and Table 1 therein, lists the MMPIs currently in clinical development.

Brief description of the invention.

Although matrix metalloproteinase inhibitors (MMPIs) are disclosed for applications where such matrix metalloproteinase enzymes such as collagenase-1, stromelysin-1 and 72kDa-gelatinase, or cytokines such as tumour necrosis factor-alpha are the major causative mechanism, the art, for example WO 93/13741, also contains speculative claims suggesting that such inhibitors might be useful in inflammation and hyperplasia conditions such as psoriasis. None of these publications exemplify topical administration of the MMPI compounds identified herein, in treating psoriasis.

The present invention is based on the finding that certain matrix metalloproteinase inhibitors when administered in a topical formulation are effective in treating psoriatic diseases.

Description of the Invention

In a first aspect of the invention, there is provided the use of a compound selected from the group consisting of:

i). N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide;

ii). [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide;

iii). 2,2-Dimethyl-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-thiomorpholine-3R-carboxylic acid hydroxyamide;

iv). 4[4'-Chloro-biphenyl-4-yl)-4-oxo-2S-(phenylsulfanylmethyl-butyric acid;

v). *N*-Hydroxy-2R-[4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-butyramide;

vi). 4-Cyclopentyl-*N*-hydroxy-3R-piperidin-1-yl-2S-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyramide;

vii). 4-[4-(4-Chloro-phenoxy)-benzenesulfonylmethyl]-tetrahydro-pyran-4-carboxylic acid hydroxyamide, and pharmaceutically or veterinarily acceptable salts thereof, in the preparation of an agent for topical administration to a patient afflicted with psoriasis.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

Aside from [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide, which is disclosed in Example 2 of WO-A-90/05719), the MMPIs for use in the invention are specifically disclosed in Table 1 of Beckett and

Whittaker (Exp. Opin. Ther. Patents 8(3):259-282, 1998). The reader is referred thereto for details of the structures of the compounds disclosed, and to the cross-referenced patents disclosed therein, which describe the methods for the preparation of the compounds.

Another aspect of this invention concerns a method for the treatment of psoriasis in mammals, particularly in humans, which method comprises the topical administration to the mammal of an effective dose of a compound selected from the group consisting of:

i). N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide;

ii). [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide;

iii). 2,2-Dimethyl-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-thiomorpholine-3R-carboxylic acid hydroxyamide;

iv). 4[4'-Chloro-biphenyl-4-yl)-4-oxo-2S-(phenylsulfanylmethyl-butyric acid;

v). *N*-Hydroxy-2R-[4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-butyramide;

vi). 4-Cyclopentyl-*N*-hydroxy-3R-piperidin-1-yl-2S-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyramide;

vii). 4-[4-(4-Chloro-phenoxy)-benzenesulfonylmethyl]-tetrahydro-pyran-4-carboxylic acid hydroxyamide, and pharmaceutically or veterinarily acceptable salts thereof.

The preferred compound for use in any aspect of the invention is N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide (disclosed in Example 10 of WO-A-94/02447) or [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide (disclosed in Example 2 of WO-A-90/05719). These compounds are referred to in the art as marimastat and batimastat respectively.

Unlike batimastat, marimastat shows good bioavailability when taken by mouth. However, chronic oral dosing of marimastat can cause musculoskeletal pain (tendonitis). Administration of marimastat by topical means may keep the amount of marimastat in systemic circulation to a level below that which has been shown to cause

this tendonitis.

In addition to batimastat and marimastat, othercompounds for use in any aspect of the invention are compounds selected from the group consisting of: 2,2-Dimethyl-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-thiomorpholine-3R-carboxylic acid hydroxyamide (**AG-3340**), 4[4'-Chloro-biphenyl-4-yl)-4-oxo-2S-(phenylsulfanylmethyl-butyric acid (**BAY 12-9566**), {disclosed in Example 196 (S isomer) of WO-A-9615096}, *N*-Hydroxy-2R-[4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-butyramide (**CGS 27023A**), 4-Cyclopentyl-*N*-hydroxy-3R-piperidin-1-yl-2S-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyramide (**Ro 32-3555**), and 4-[4-(4-Chloro-phenoxy)-benzenesulfonylmethyl]-tetrahydro-pyran-4-carboxylic acid hydroxyamide (**RS 130830**). These compounds are listed in Table 1 of Beckett and Whittaker (Exp. Opin. Ther. Patents 8(3):259-282, 1998).

In a further aspect of the invention there is provided a pharmaceutical or veterinary composition for the treatment of psoriasis by topical administration, which composition comprises at least one compound selected from the group consisting of:

i). N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide;

ii). [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide;

iii). 2,2-Dimethyl-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-thiomorpholine-3R-carboxylic acid hydroxyamide;

iv). 4[4'-Chloro-biphenyl-4-yl)-4-oxo-2S-(phenylsulfanylmethyl-butyric acid;

v). *N*-Hydroxy-2R-[4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-butyramide;

vi). 4-Cyclopentyl-*N*-hydroxy-3R-piperidin-1-yl-2S-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyramide;

vii). 4-[4-(4-Chloro-phenoxy)-benzenesulfonylmethyl]-tetrahydro-pyran-4-carboxylic acid hydroxyamide, and pharmaceutically or veterinarily acceptable salts thereof, in admixture with at least one pharmaceutically or veterinarily acceptable topically applicable carrier.

The process by which the therapeutic action occurs generally involves the diffusion and penetration of the drug into and through particular layers of the skin to give the desired pharmacological action. In psoriatic conditions, it is the germinal skin layer that becomes hyperplastic.

Studies on the permeation of drugs into and through human skin has been well reviewed (Barry B W, *Dermatological Formulations: Percutaneous Absorption*, Marcel Dekker, New York, 1983; Wester R C and Maibech H I, Percutaneous Absorption of Drugs, *Clinical Pharmacokinetics*, **23**:253-266, 1992).

The permeation of a particular drug can either be predicted or evaluated by *in-vitro* experimentation using animal or human cadaver skin. As the permeation is related to the physiochemical properties of the drug molecule it can estimated that the steady state flux (J) per unit area across the skin is given by:

$$J = DK\Delta c / l$$

where D is the diffusion coefficient through the stratum corneum, K is the skin-water partition coefficient, l is the diffusional pathlength and Δc the concentration difference between the drug in the aqueous solution (c_s) and that in the deep skin layers (c_t). As long as $c_s >> c_t$ then the equation becomes

$$J = DKc_s / l$$

It is generally desirable to have an high chemical potential in the formulation vehicle to maximise the release rate into the skin. This can usually be achieved by maximising the solubility of the drug in the vehicle. Using a saturated aqueous solution (c_{sat}) the maximum flux (J_{max}) will be obtained:

$$J_{max} = k_p c_{sat}$$

where k_p is the permeability coefficient. It has been shown (Potts and Guy, 1992) that this can be predicted from two simple physiochemical parameters of the molecule, the

octanol-water partition coefficient (K_{oct}) and its molecular weight (MW).

The above predictive method has not yet been shown to be applicable to every type of compound and so it is also useful to experimentally determine some values for flux by *in-vitro* studies using human skin.

In order to interpret the flux data from *in-vitro* studies and thus improve the formulation it is usually better to evaluate simple solution formulations first. The solvent or solvent mixture chosen is normally based on that giving the desired concentration from experiment or solubility prediction (Valvani and Yalkowsky; *J. Pharm. Sci.*, **69**:912-922, 1980;Vaughan C D, *J. Soc. Cosmet. Chem.*, **36**:319-333, 1985) combined with its ability to give chemical and physical stability to the active substance. The individual solvents are chosen for evaluation from a list of commonly used excipients in cosmetic and pharmaceutical as can be found in the CTFA Cosmetic Ingredient Handbook, 2nd Edition, Editor Wenniger J A, CTFA (1992), or from The Handbook of Pharmaceutical Excipients, 2nd Edition, Royal Pharmaceutical Society.

The initial topical formulations can therefore be based on these solutions to make pharmaceutically acceptable products. An example of this type of product is an alcoholic solution of the active which has been gelled using an hydroxypropylcellulose polymer.

Other commonly acceptable solvents and polymers known in the prior art may also be used in a similar manner. It may also be possible to use other excipients that produce gels such as the Pluronic® range of materials.

The range of products that are feasible, in addition to gels, for the stated compounds are all those that are well known to the person skilled in the art such as liquids, lotions, creams, ointments, pastes, powders and the range of excipients used in these can be chosen from those well known in the art to either maximise solubility of the product or to stabilise the active product with respect to chemical and physical characteristics. It is also normal to consider the need for microbiological preservation and other factors related to the cosmetic appeal of the product to the patient to enhance product use

compliance.

The processes for the manufacture of a topical formulation according to the invention are again based on the methods commonly practised in the art, such as the preparation of simple excipient mixtures by physical or thermal action or the preparation of more complex structures within the product such as liposomes.

The dosage for topical administration will of course depend on the size of the area being treated. The concentration of the active ingredient in the topical formulation will usually be in the range of 0.01 - 5%, preferably 0.1 to 2%, more preferably 0.5 to 1%. The inventors have surprisingly found that a topical gel formulation containing 1% marimastat delivered six-fold more drug into the skin after 48 hours than did the equivalent 0.1% gel ($0.2\pm0.1\mu g/cm^2$).

In a preferred embodiment, the active ingredient will diffuse through the skin and become concentrated at the affected skin layer at a dosage sufficient to impart a beneficial anti-psoriatic effect, whereas diffusion through and entry into the systemic circulation of the active ingredient will be, in increasing order of preference, less than 90%, 80%, 70%, 60%, 50%, 40% 20% 10% and 1% of the amount reaching the affected skin layer.

The preferred topical formulation comprises the active ingredient (MMPI) in a gel comprising a 50:50 mix of ethanol:propyleneglycol with 2% polymer (hydroxypropylcellulose (Klucel HF) Ph. Eur). To improve drug uptake into the skin, this composition can optionally also contain DMSO, preferably at 0.9%. The inventors have found that inclusion of 0.9% DMSO into a 0.1% topical formulation of marimastat increased the drug uptake by the skin approximately two fold.

The following examples illustrates the invention, but are not intended to limit the scope in any way.

Example 1

Marimastat (N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide) is disclosed in Example 10 of WO-A-94/02447.

Marimastat was formulated at three concentrations 0.1% , 0.3% and 1%.

The 0.1% formulation for topical administration to psoriatic areas comprised 0.1% marimastat, 48.95% w/w ethanol, 48.95%w/w propyleneglycol and 2% hydroxypropylcellulose (Klucel HF) Ph. Eur.

The 0.3% formulation for topical administration to psoriatic areas comprised 0.3% marimastat, 48.85% w/w ethanol, 48.85%w/w propyleneglycol and 2% hydroxypropylcellulose (Klucel HF) Ph. Eur.

The 1% formulation for topical administration to psoriatic areas comprised 1% marimastat, 48.5% w/w ethanol, 48.5%w/w propyleneglycol and 2% hydroxypropylcellulose (Klucel HF) Ph. Eur.

Efficacy assessments for psoriasis treatments are evaluated using the "Psoriasis Area and Severity Index" (PASI) scoring system (Fredrikkson and Pettersson. Dermatologica. 157:238-244, 1978; Fredrikkson et al., Int. J. Dermatol. 22:536-540, 1983), assessing the severity (erythema, induration and scaling) of skin lesions at days 0, 14, 28, 42, 56 and 84.

Four patients with the 0.1% topical gel formulation and three patients with the 1% topical gel formulation were instructed to apply the gel to all affected areas (except the head), twice a day for 42 continuous days, commencing Day 0. Patients were assessed for psoriasis severity at screening, before treatment (Day 0; 14 ± 3days after screening) and at Days 14, 28, and 42 during treatment. Patients were then assessed after discontinuation of treatment at Day 56 and Day 84. Treatment with both 0.1% and 1% formulations were found to reduce the severity of the psoriatic lesions (Figure 1). The 1% gel appeared to confer a greater relative reduction in the severerity of the

lesions and a more visible stabilisation of the disease state after cessation of administration.

Interestingly, independent testing of both concentrations of gel in art recognised *in vitro* skin permeation and uptake models using Franz-type diffusion cells, demonstrated that the 1% gel delivered approximately six times more marimastat (1.2±0.2μg/cm^2) into the skin after 48 hours than did the equivalent 0.1% gel (0.2±0.1μg/cm^2). Inclusion of 0.9% DMSO into the 0.1% formulation increased marimastat uptake by the skin approximately two fold.

Confirmation of the effectiveness of topically administered marimastat was also obtained from a phase II, randomized, double-blind, vehicle-controlled, dose-finding, left-right comparative study assessing the efficacy and safety of topical marimastat in patients with bilateral, symmetrical chronic plaque-type psoriasis.

For each patient the study was in two phases. In phase 1, patients were instructed to apply one of two gels (marimastat or vehicle) to either their left- or right-sided target plaque and to apply the other gel to the contralateral plaque twice a day for 42 days commencing day 0. In phase 2, the preferred treatment was continued, double-blind, for a further 42 days with application to all psoriatic plaques (except those on the face or scalp). Three concentrations of marimastat gel were studied in sequential groups of 12 patients. The first 12 patients received 0.1% marimastat gel, the second 0.3% and the third group 1% gel. Efficacy was determined by (i) the severity of erythema, induration and scaling of the left-right target plaques during treatment phase 1, (ii) the dimensions of target plaques and (iii) changes in PASI scores calculated from all plaques (excluding the head) from Day 42 of phase 1 to Day 84.

Example 2.

Testing topically administered MMPI compounds in the murine model of dermal inflammation and hyperproliferation.

Although not fully reproducing the human psoriatic condition, the murine model of dermal inflammation and hyperproliferation (see for example Holleran *et al.*, Arch.

Dermatol. Res. 289:138-144, 1997; or, Griffiths *et al.* Agents and Actions. 25(3/4):344-351, 1988) or the following adaptated model wherein TPA is used to induce inflammation, oedema and hyperplasia in the ear, is an art recognised model of psoriasis. Positive results, with the test MMPI compounds identified below, in either of these models, predicts that these compounds will be useful in treating psoriasis by topical administration.

Adapted model.

Groups of BALB/c(♀) mice are challenged with 5µg TPA (12-O-tetradeconoylphorbol-13-acetate) in Acetone, in 20µl dose volume (10µl on each side) on the right ear under light halothane anaesthesia. The contra-lateral ear is treated with acetone solvent only.

Ear thickness was measured using micro-calipers (Mitutoyo, Japan) at 0, 6, 24, 30 and 48 hours post TPA application under light halothane anaesthesia.

The test compounds are administered topically in 10µl dose volume per side of the ear at 6, 24 and 30 hour time-points immediately following the thickness measurement. The test agent was applied 6 hours after TPA administration as this period is necessary for the TPA-induced psoriasis-like effects, such as oedema,to become established.

Test compounds:

1. 2,2-Dimethyl-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-thiomorpholine-3R-carboxylic acid hydroxyamide (**AG-3340**);
2. 4[4'-Chloro-biphenyl-4-yl)-4-oxo-2S-(phenylsulfanylmethyl-butyric acid (**BAY 12-9566**);
3. *N*-Hydroxy-2R-[4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-butyramide (**CGS 27023A**);
4. 4-Cyclopentyl-*N*-hydroxy-3R-piperidin-1-yl-2S-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyramide (**Ro 32-3555**);
5. 4-[4-(4-Chloro-phenoxy)-benzenesulfonylmethyl]-tetrahydro-pyran-4-carboxylic acid hydroxyamide (**RS 130830**); and,
6. 4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide (**batimastat**).

Claims

1. The use of a compound selected from the group consisting of:

i) N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide;

ii) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide;

iii) 2,2-Dimethyl-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-thiomorpholine-3R-carboxylic acid hydroxyamide;

iv) 4[4'-Chloro-biphenyl-4-yl)-4-oxo-2S-(phenylsulfanylmethyl-butyric acid;

v) *N*-Hydroxy-2R-[4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-butyramide;

vi) 4-Cyclopentyl-*N*-hydroxy-3R-piperidin-1-yl-2S-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyramide;

vii) 4-[4-(4-Chloro-phenoxy)-benzenesulfonylmethyl]-tetrahydro-pyran-4-carboxylic acid hydroxyamide, and pharmaceutically or veterinarily acceptable salts thereof, in the preparation of an agent for topical administration to a patient afflicted with psoriasis.

2. A method for the treatment of psoriasis in mammals, particularly in humans, which method comprises the topical administration to the mammal of an effective dose of a compound selected from the group consisting of:

i) N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide;

ii) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide;

iii) 2,2-Dimethyl-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-thiomorpholine-3R-carboxylic acid hydroxyamide;

iv) 4[4'-Chloro-biphenyl-4-yl)-4-oxo-2S-(phenylsulfanylmethyl-butyric acid;

v) *N*-Hydroxy-2R-[4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-butyramide;

vi) 4-Cyclopentyl-*N*-hydroxy-3R-piperidin-1-yl-2S-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyramide;

vii) 4-[4-(4-Chloro-phenoxy)-benzenesulfonylmethyl]-tetrahydro-pyran-4-carboxylic acid hydroxyamide, and pharmaceutically or veterinarily acceptable salts thereof.

3. A pharmaceutical or veterinary composition for the treatment of psoriasis by topical administration, which composition comprises at least one compound selected from the group consisting of:

i) N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide;

ii) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide;

iii) 2,2-Dimethyl-4-[4-(pyridin-4-yloxy)-benzenesulfonyl]-thiomorpholine-3R-carboxylic acid hydroxyamide;

iv) 4[4'-Chloro-biphenyl-4-yl)-4-oxo-2S-(phenylsulfanylmethyl-butyric acid;

v) *N*-Hydroxy-2R-[4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-butyramide;

vi) 4-Cyclopentyl-*N*-hydroxy-3R-piperidin-1-yl-2S-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyramide;

vii) 4-[4-(4-Chloro-phenoxy)-benzenesulfonylmethyl]-tetrahydro-pyran-4-carboxylic acid hydroxyamide, and pharmaceutically or veterinarily acceptable salts thereof, in admixture with at least one pharmaceutically or veterinarily acceptable topically applicable carrier.

4. A use according to claim 1, a method according to claim 2, or a pharmaceutical or veterinary composition as claimed in claim 3, wherein the compound is N^2-[3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-tert-leucine-N^1-methylamide.

5. A use according to claim 1, a method according to claim 2, or a pharmaceutical or veterinary composition as claimed in claim 3, wherein the compound is [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide.

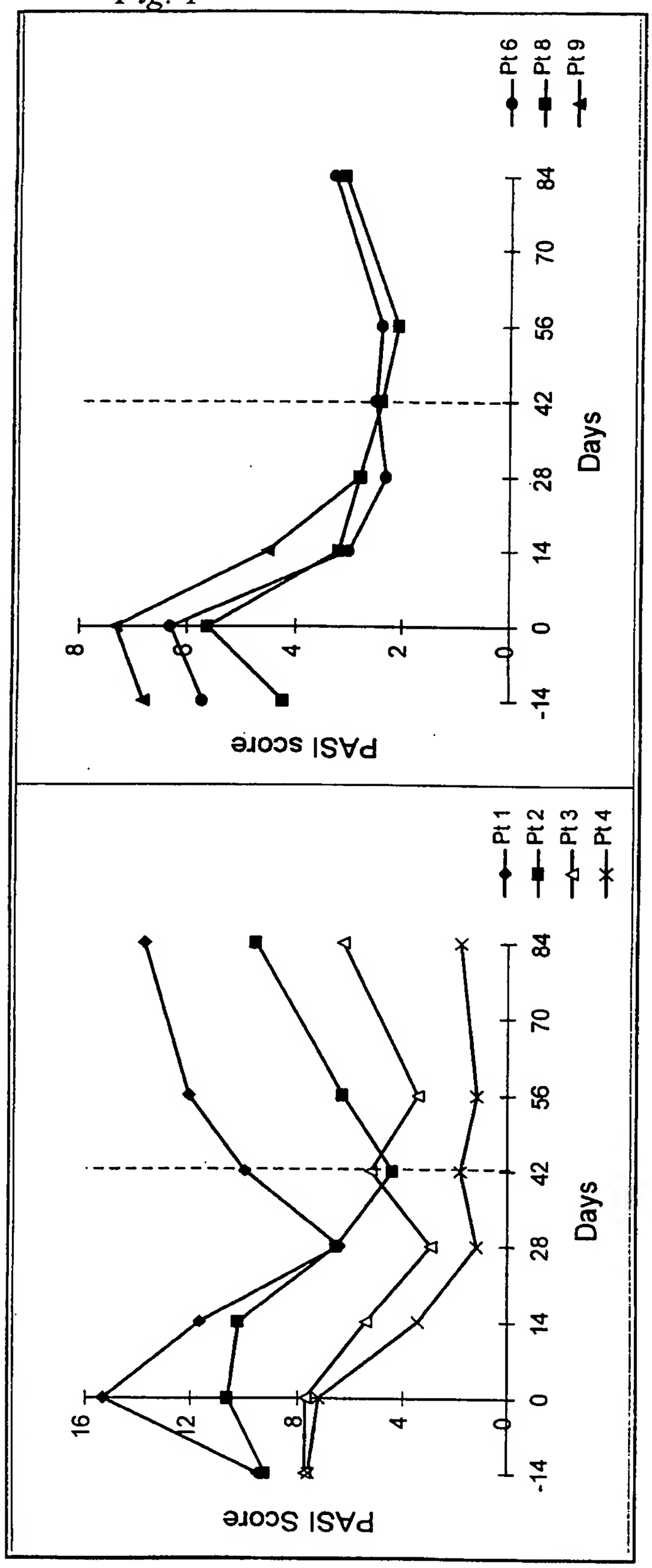
6. A use according to claim 1, a method according to claim 2, or a pharmaceutical or veterinary composition as claimed in claim 3,wherein the compound is present at a

concentration of 1%.

7. A use, a method, or a pharmaceutical or veterinary composition as claimed in claim 4, wherein the compound is present at a concentration of 1%.

8. A pharmaceutical or veterinary composition as claimed in any of claims 3 to 8, which composition contains DMSO, preferably at 0.9%.

Fig. 1


1% Marimastat Gel
Pt 6
Pt 8
Pt 9
PASI score
Days
0.1% Marimastat Gel
Pt 1
Pt 2
Pt 3
Pt 4
PASI Score
Days